EVALUATION OF CARDIOVASCULAR FUNCTION IN OVERT AND SUBLINICAL HYPOTHYROIDISM

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CERTIFICATE

This is to certify that this dissertation entitled **"EVALUATION OF CARDIOVASCULAR FUNCTION IN OVERT AND SUBLINICAL HYPOTHYROIDISM"** submitted by Dr**.** J.JACINTH PREETHI, appearing for Part II M.D.Branch I General Medicine Degree examination in April 2012 is a bonafide record of work done by her under my direct audience and supervision in partial fulfillment of regulations of the Tamil Nadu Dr. M.G.R. Medical University, Chennai. I forward this to the Tamil Nadu Dr.M.G.R. Medical University, Chennai, Tamil Nadu, India.

Prof.A.RADHAKRISHNAN, M.D.,
Professor of Medicine, Guide & Supervisor,
Institute of internal medicine,
MMC & RGGGH,
Chennai – 600 003

Prof.C.RAJENDIRAN, M.D.,
Director and Professor,
Institute of Internal Medicine,
MMC & RGGGH,
Chennai – 600 003.

DR.V.KANAGASABAI,M.D.,
D E A N
Madras Medical College and
Rajiv Gandhi Government General Hospital,
Chennai – 600003.

DECLARATION

I solemnly declare that this dissertation entitled "**EVALUATION OF CARDIOVASCULAR FUNCTION IN OVERT AND SUBLINICAL HYPOTHYROIDISM**" was done by me at Madras Medical College and Government General Hospital, during the academic year 2009-2012 under the guidance and supervision of **Prof.A.Radhakrishnan M.D**. This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University towards the partial fulfillment of requirements for the award of M.D. Degree in General Medicine (Branch-I).

Place: Chennai. Signature of the candidate

Date:

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ABBREVIATIONS

ASE- American society of echocardiography

BMI – Body mass index

DM- Diabetes mellitus

EDV- End diastolic volume

EF- Ejection fraction

ESV- End systolic volume

FS-Fractional shortening

HDL- High density lipoprotein

IVSW- Inter ventricular septal wall

LDL-Low density lipoprotein

LV- Left ventricle

LVEF- Left ventricular ejection fraction

LVID (D)- Left ventricular internal diameter (diastolic)

LVID(S)- Left ventricular internal diameter (systolic)

LVPW- Left ventricular posterior wall

T3- triiodothyronine

T4- thyroxine

TSH- Thyroid stimulating hormone

INTRODUCTION

INTRODUCTION

The thyroid gland maintains the level of metabolism in the tissues that is optimal for their normal function. The function of the thyroid is to generate the quantity of thyroid hormone necessary to meet the demands of the peripheral tissues. The principal hormones secreted by the thyroid are **thyroxine (T_4)** and **triiodothyronine (T_3)**. T_3 is also formed in the peripheral tissues by deiodination of T_4. Both hormones are iodine-containing amino acids. Small amounts of reverse triiodothyronine (3, 3′, 5′-triiodothyronine, RT_3) and other compounds are also found in thyroid venous blood. T_3 is more active than T_4, whereas RT_3 is inactive.

Anatomy

The thyroid is one of the largest of the endocrine organs, weighing approximately 15 to 20 g. The normal thyroid is made up of two lobes joined by a thin band of tissue, the isthmus. The gland is composed of closely packed spherical units termed *follicles,* which are invested with a rich capillary network. The interior of the follicle is filled with the clear proteinaceous colloid that normally is the major constituent of the total thyroid mass [(1)].

Thyroid Hormone Synthesis

The thyroid cell membranes facing the capillaries contain a **symporter,** or iodide pump, that transports Na^+ and I^- into the cells against the electrochemical gradient for I^-. This Na^+/I^- symporter (NIS) is capable of producing intracellular I^- concentrations that are 20-40 times as great as the concentration in plasma.

In the thyroid gland, iodide is oxidized to iodine .In the process of hormone synthesis; the first product is monoiodotyrosine (MIT). MIT is next iodinated in the 5 position to form diiodotyrosine (DIT). Two DIT molecules then undergo an oxidative condensation to form T_4 with the elimination of the alanine side chain from the molecule that forms the outer ring. Thyroid peroxidase is probably involved in coupling as well as iodination. T_3 is probably formed by condensation of MIT with DIT. A small amount of RT_3 is also formed, probably by condensation of DIT with MIT and bound to the 3 position of tyrosine residues that are part of the thyroglobulin molecule in the colloid.(2)

Secretion

The human thyroid secretes about 80 ug (103 nmol) of T_4, 4 ug (7 nmol) of T_3, and 2 ug (3.5 nmol) of RT_3 per day .However, MIT and DIT are not secreted. The iodinated tyrosines are deiodinated by a microsomal **iodotyrosine deiodinase.**(2)

Transport & Metabolism

The plasma proteins that bind thyroid hormones are **albumin;** a prealbumin formerly called **thyroxine-binding prealbumin (TBPA)** and now called **transthyretin;** and a globulin with an electrophoretic mobility between those of α_1- and α_2-globulin, **thyroxine-binding globulin (TBG).** Of the three proteins, albumin has the largest **capacity** to bind T_4—ie, it can bind the most T_4 before becoming saturated—and TBG has the smallest capacity.

Mechanism of Action

Thyroid hormones enter cells, and T_3 binds to thyroid receptors (TR) in the nuclei. T_4 can also bind, but not as avidly. The hormone-receptor complex then binds to DNA via zinc fingers and increases or in some cases decreases the expression of a variety of different genes that code for enzymes which regulate cell function. Thus, the nuclear receptors for thyroid hormones are members of the super family of hormone-sensitive nuclear transcription factors. There are two human TR genes: an α receptor gene on chromosome 17 and β receptor gene on chromosome 3.

Effects on the Cardiovascular System

Thyroid hormone transcriptionally regulates many cardiac proteins the thyroid hormone exerts most of its direct effects on cardiac contractility by regulating calcium cycling through the SERCA-phospholamban system.

Thyroid hormone is an important regulator of cardiac function and cardiovascular hemodynamics. T(3) the physiologically active form of thyroid hormone, binds to nuclear receptor proteins and mediates the expression of several important cardiac genes, inducing transcription of the positively regulated genes including alpha-myosin heavy chain (MHC) and the sarcoplasmic reticulumcalcium ATPase. Negatively regulated genes include beta-MHC and phospholamban, which are down regulated in the presence of normal serum levels of thyroid hormone. T3 mediated effects on the systemic vasculature include relaxation of vascular smooth muscle resulting in decreased arterial resistance and diastolic blood pressure. In hyperthyroidism, cardiac contractility and cardiac output are enhanced and systemic vascular resistance is decreased, while in hypothyroidism, the opposite is true. Patients with subclinical hypothyroidism manifest many of the same cardiovascular changes, but to a lesser degree than that which occurs in overt hypothyroidism [(3)].

An understanding of pathophysiology of cardiovascular changes of the thyroid enables prevention, early diagnosis and prompt intervention to control complications. Also the presence of cardiovascular complications may necessitate institution of therapy in patients of asymptomatic subclinical hypothyroidism.

AIM AND OBJECTIVE

AIM OF THE STUDY

The aim of this study is to assess

i. The cardiovascular functions in primary overt and subclinical hypothyroid patients.

ii. To find a correlation between severity of disease and presence of significant echocardiographic changes.

REVIEW OF LITERATURE

REVIEW OF LITERATURE

Thyroid diseases are among the commonest endocrine disorders worldwide. India, is no exception. There are various causes of primary hypothyroidism, but autoimmune disease (Hashimoto's thyroiditis) and thyroid failure following I 131 or surgical treatment account for over 90% of cases in those parts of the world which are not significantly iodine-deficient. Iodine deficiency as a cause of hypothyroidism is more common in developing countries.

The terminology 'subclinical hypothyroidism' was probably first used by Evered and colleagues to describe a group of individuals in whom 'conventional tests of thyroid function showed nothing abnormal ... but they were all found to have a raised serum TSH concentration' (Evered *et al*., 1973). Subclinical hypothyroidism is defined today by normal serum free T4 levels and serum TSH levels above the upper limit of the reference range.

The clinical implications of subclinical hypothyroidism have provoked controversy. The progression to overt hypothyroidism is approximately 2–5% per year. Vanderpump MP et al in a follow up study states the rate of progression is proportional to baseline TSH concentration and is higher in individuals with antithyroid antibodies (4). Because of the high prevalence of subclinical hypothyroidism and its possible associations with cardiovascular disease,

dyslipidaemia and a host of other problems, as well as progression to overt hypothyroidism, it is important to screen the general population and treat appropriate patients.

According to a survey by N. Kochupillai the countrywide prevalence of thyroid disorders is 42 millions. [5] Jayarama, K. S. et al the prevalence of hypothyroidism in India is 0.071 %.[6]. In a population-based study done in Cochin on 971 adult subjects, the prevalence of hypothyroidism was 3.9%. The prevalence of subclinical hypothyroidism was also high in this study, the value being 9.4%. In women, the prevalence was higher, at 11.4%, when compared with men, in whom the prevalence was 6.2%. [7] The worldwide prevalence of subclinical hypothyroidism ranges from 1% to 10%; the highest age and sex specific rates are in woman over 60 years, approaching to 20% [8, 9].

According to a study by Jangid DR et al thyroid surgery and decompensated iodine deficiency were the major known causes of hypothyroidism (19.5% and 15.3% respectively), while in the majority of patients (45.14%) the aetiology was obscure.[10]

A review article by Shikha Bharaktiya states that the frequency of hypothyroidism, goiters, and thyroid nodules increases with age. Hypothyroidism is most prevalent in elderly populations, with 2% to as much as 20% of older age

groups having some form of hypothyroidism. The Framingham study found hypothyroidism (TSH >10 mIU/L) in 5.9% of women and 2.4% of men older than 60 years [11].

Causes of hypothyroidism

Primary Hypothyroidism

Acquired

Hashimoto's thyroiditis

Iodine deficiency (endemic goiter)

Drugs blocking synthesis or release of T_4 (e.g., lithium, ethionamide, sulfonamides, iodide)

Goitrogens in foodstuffs or as endemic substances or pollutants

Cytokines (interferon-α, interleukin-2)

Thyroid infiltration (amyloidosis, hemochromatosis, sarcoidosis, Riedel's struma, cystinosis, scleroderma)

Postablative due to ^{131}I, surgery, or therapeutic irradiation for nonthyroidal malignancy

Congenital

Iodide transport or utilization defect (NIS or pendrin mutations)

Iodotyrosine dehalogenase deficiency

Organification disorders (TPO* deficiency or dysfunction)

Defects in thyroglobulin synthesis or processing

Thyroid agenesis or dysplasia

TSH receptor* defects

Thyroidal Gs protein abnormalities (pseudohypoparathyroidism type 1a)

Idiopathic TSH unresponsiveness

Transient (Post-thyroiditis) Hypothyroidism

Following subacute, painless, or postpartum thyroiditis

Consumptive Hypothyroidism

Rapid destruction of thyroid hormone due to D3 expression in large hemangiomas or hemangioendotheliomas

Defects of Thyroxine to Triiodothyronine Conversion

Selenocysteine insertion sequence–binding protein (SECIS-BP2) defect

Drug-Induced Thyroid Destruction

Tyrosine kinase inhibitor (sunitinib)

Central Hypothyroidism

Acquired

Pituitary origin (secondary)

Hypothalamic disorders (tertiary)

Bexarotene (retinaid X receptor agonist)

Dopamine and/or severe illness

Congenital

TSH deficiency or structural abnormality

TSH receptor defect

Resistance to Thyroid Hormone

Generalized

“Pituitary” dominant

Signs and Symptoms of Hypothyroidism (Descending Order of Frequency)

Symptoms

Tiredness, weakness

Dry skin

Feeling cold

Hair loss

Difficulty concentrating and poor memory

Constipation

Weight gain with poor appetite

Dyspnea

Hoarse voice

Menorrhagia (later oligomenorrhea or amenorrhea)

Paresthesia

Impaired hearing

Signs

Dry coarse skin; cool peripheral extremities

Puffy face, hands, and feet (myxedema)

Diffuse alopecia

Bradycardia

Peripheral edema

Delayed tendon reflex relaxation

Carpal tunnel syndrome

Serous cavity effusions

Cardiac involvement in myxedema was first described by Zondek in 1918[12].The cardiovascular findings of hypothyroidism are more subtle. The clinical presentation of overt hypothyroidism is not obvious and most patients have few symptoms and signs [13].The CVS manifestations of hypothyroidism include the following:

a) Reduced total intravascular volume

b) Reduced contractility

c) Reduced heart rate (All leading to decreased cardiac output)

d) Raised systemic vascular resistance (leading to increased diastolic blood pressure)

e) Raised capillary permeability (leading to pericardial effusion)

Bradycardia and systemic hypertension, with narrow pulse pressure and slightly increased mean arterial pressure, and some degree of exercise impairment are the most-common findings in patients with overt hypothyroidism [13, 14].

No specific pathophysiological changes can be identified that characterize the myxedema heart. The cardiac silhouette is enlarged; however, heart weight is usually normal. Cardiac papillary muscle shows a depression of the force velocity curve and reduced rate of tension development, indicating significant contractile abnormalities. Myofibril swelling with loss of striation and some degree of interstitial fibrosis occurs on histological examination of hypothyroid hearts. In addition, accumulation of mucopolysaccharides can be demonstrated.

INTERACTION OF THYROID HORMONES WITH THE SYMPATHETIC NERVOUS SYSTEM

Some clinical manifestations of hypothyroidism such as sinus bradycardia are suggestive of decreased sympathetic tone. But the catecholamine

concentrations are normal or decreased in hyperthyroidism and elevated in hypothyroidism.[15-17] The latter finding is not related to decreased norepinephrine clearance but rather to increased norepinephrine release from sympathetic nerves.[17]. This interpretation is strengthened by the observation that thyrotropin releasing hormone (TRH),which is elevated in primary hypothyroidism, directly stimulates sympathetic outflow within the central nervous system and may be taken up by nerve endings to serve as a neurotransmitter. This apparent paradox of clinical signs evoking decreased sympathetic tone in the presence of elevated norepinephrine release from sympathetic nerve endings is consistent with the hypothesis of desensitization to the effects of catecholamines in hypothyroidism. [18].

HYPERTENSION

Three factors contribute to systemic hypertension in overt hypothyroidism. The first is the increase in peripheral vascular resistance [13] , the second is the increase in arterial stiffness, which likely results from myxedema of the arterial wall [19, 20] and the third is endothelial dysfunction. Systemic hypertension associated with overt hypothyroidism is poorly controlled by conventional treatments, whereas it promptly improves with achievement of euthyroidism [21].

Ikuo Saito et al in his study showed hypertension is more often associated with hypothyroidism than euthyroidism in patients over 50 years old, and that blood pressure is often reduced in response to adequate thyroid hormone replacement therapy alone [22]

LV FUNCTION

The most-consistent cardiac abnormality recognized in patients with overt hypothyroidism is impairment of LV diastolic function, which is characterized by slowed myocardial relaxation and impaired early ventricular filling [20, 23]. This is completely reversed by replacement therapy.

Bernadette Biondi et al in a study evaluated 26 patients (mean age, 36 yr) by Doppler-echocardiography, whereas a subgroup of 10 patients, randomly selected, were reevaluated after 6 months of L-T4 substitutive therapy. Echocardiogram examination showed no abnormalities of the left ventricular morphology and a slight, but not significant, reduction in the systolic function in the patient group. In contrast, Doppler derived indices of diastolic function showed significant prolongation of the isovolumic relaxation time, increased A wave and reduced early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio.In the subgroup of 10 patients, thyroid hormone profile was normalized by 6 months of L-T4 substitutive therapy, whereas no changes were observed in the left

ventricular morphology. Assessment of diastolic function showed significant shortening of isovolumic relaxation time, reduction of A wave, and increase of early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio. These findings indicate that subclinical hypothyroidism affects diastolic function and that this abnormality may be reversed by L-T4 substitutive therapy. [24]

LV systolic function usually is only marginally subnormal, as demonstrated by slightly reduced values of ejection fraction and stroke volume [20, 21]. Systolic function has been evaluated in overt and subclinical hypothyroidism by different techniques. All showed the abnormalities reverting on replacement therapy.

PERICARDIAL EFFUSION

Pericardial effusions can occur consistent with observation that patients with hypothyroidism have an increase in volume of distribution of albumin and a decrease in lymphatic clearance function. Occasionally the pericardial effusions are quite large, causing the appearance of cardiomegaly on chest radiograph. Although rare, tamponade with hemodynamic compromise can occur. Echocardiography demonstrates small to moderate effusions in up to 30 percent of overtly hypothyroid patients, which resolve over a period of weeks to months after initiation of thyroid hormone replacement.[13] The fluid usually has a high

cholesterol and protein content and is sometimes described as resembling 'gold paint'.

Kerber and Sherman [25] found echocardiographic evidence of pericardial effusion in 10 of 33 patients with hypothyroidism. Hardisty CA, Naik DR, Munro DS. studied 39 patients with untreated hypothyroidism using echocardiography for the presence of a pericardial effusion. Effusions were present in twelve patients who tended to be more severely hypothyroid. 9 were reinvestigated during thyroxine replacement therapy and the effusions did not disappear until thyroid function tests had returned to normal. [26]

LV MASS

Overt hypothyroidism may be associated with some increase in LV mass. In both hypothyroidism and myxedema, reversible diastolic abnormalities have been reported. In an echocardiographic study, asymmetric septal hypertrophy was found in 17 of 19 patients, and some of them had echocardiographic features similar to those found in hypertrophic obstructive cardiomyopathy. In 10 such patients, this abnormality resolved on return to euthyroid state. There is no good explanation for this finding that has been confirmed on postmortem examinations and may represent one potential cause of left ventricular diastolic dysfunction in hypothyroid patients. [27]

ANGINA

The increase in peripheral vascular resistance and arterial stiffness in overt hypothyroidism contributes to increased cardiac after load. This causes a disproportionate increase in myocardial oxygen uptake with respect to the level of cardiac performance explains in part why overt hypothyroidism may precipitate or worsen angina in patients with suspected or known ischemic heart disease [28] and why some of these patients have an improvement in anginal symptoms after thyroid hormone replacement is initiated.

Raised serum cholesterol level and other lipid abnormalities are known to occur in patients with hypothyroidism. Agdeppa er al.[29]) found that high-density lipoprotein cholesterol (HDL-C) levels are reduced and low density lipoprotein cholesterol (LDL-C) levels are increased in hypothyroidism. The ratio between LDL-C and HDL-C is high in hypothyroid patients. According to Steinberg [30] ischemic heart disease is more prevalent among hypothyroid patients when hypertension is present.

HEART FAILURE

Hypothyroidism may also rarely be the sole cause of heart failure. One such case has been reported.[31] A low heart rate, decreased myocardial contractility, and increased peripheral resistance can all lead to low cardiac output. Furthermore, left

ventricular filling may be impaired by the simultaneous presence of left ventricular hypertrophy, abnormal relaxation, and bradycardia. Heart failure may occur [32-34] when peripheral metabolic demand cannot be matched by an adequate cardiac output. In addition, cardiac tamponade may be a rare cause of cardiac failure in myxedematous patients.[35] Heart failure is, however, more common in patients with underlying coronary artery disease Heart failure may be the result of patchy myocardial necrosis or ongoing ischemia, which may worsen at the time of thyroid replacement therapy, due to increased myocardial oxygen demand in the face of decreased coronary reserve.

ECG

ECG in hypothyroidism is characterized by sinus bradycardia, low voltage, right bundle branch block (RBBB), flat or inverted T wave and prolongation of the action potential duration and the QT interval. The latter in turn predisposes the patients to ventricular arrhythmias, and cases of patients with acquired torsades de pointes that have improved or completely resolved with thyroid hormone replacement have been reported [36]

LIPID ABNORMALITIES

Both the synthesis and the degradation of lipid are depressed in hypothyroidism. Degradation, however, is reduced to a greater extent, with a net

effect of accumulation of LDL and triglycerides [37].HDL concentrations are reduced. Plasma free fatty acid levels are decreased, and the mobilization of free fatty acids in response to fasting, catecholamines, and growth hormone is impaired. All of these abnormalities are relieved by treatment.

Patrícia De Fátima et al performed, a cross-sectional study with 226 participants [subclinical hypothyroidism (SH) = 133 participants, manifest hypothyroidism (MH) = 23 participants, and euthyroidism (EU) = 70 participants]. The mean levels of atherogenic lipid variables were greater in MH than in SH and were greater in SH than in EU, although the differences between SH and EU did not reach statistical significance. The SH subgroup with greater serum thyrotropin (TSH) levels and that with positive antithyroperoxidase antibodies (TPO-Ab) had greater levels of triglycerides and of the atherogenic index Apo B/Apo A. A positive correlation exists between serum TSH and total cholesterol (rs = 0.167; $P = 0.006$), triglycerides (rs = 0.219; $P < 0.001$), and ApoB levels (rs = 0.205; $P < 0.001$). [38]

Subclinical hypothyroidism does result in a small increase in LDL cholesterol and a decrease in high-density lipoprotein cholesterol, changes that enhance the risk for development of atherosclerosis and coronary artery disease.

Ganotakis ES at al studied the frequency and type of lipid disorders associated with subclinical hypothyroidism (SH) in older women .Fasting serum lipid profiles and thyroid function tests were measured in 333 apparently healthy women (mean age: 71.8 +/- 7 years). Low-density lipoprotein cholesterol (LDL-C) concentrations were higher in the women with SH ($p = 0.037$). The mean values of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), TC/HDL-C ratio, lipoprotein (a) (Lp[a]), apolipoprotein A-I (apo AI) apolipoprotein B100 (apo B) and apo B/apo A ratio were higher and triglycerides (TG) were lower, compared with those with normal levels of thyrotropin. Restoration of euthyroid status (thyroxine: 50-100 microg/day) in 17 SH women significantly improved TC ($p = 0.017$), LDL-C ($p = 0.014$), TC/HDL-C ($p = 0.05$), LDL-C/HDL-C ($p = 0.03$), apo B ($p = 0.013$), and Lp(a) ($p = 0.0005$) values. Thyroid hormone replacement therapy significantly improved serum lipids. In particular, the reduction in LDL-C and Lp(a) concentrations may be of clinical benefit[39]

SUBCLINICAL HYPOTHYROIDISM

Subclinical hypothyroidism is defined by elevated serum TSH level in the presence of normal levels of free thyroid hormones. Up to two thirds of patients have serum TSH between 5–10 mU/L and thyroid autoantibodies [40,41]. Almost half of these individuals may progress to overt thyroid failure [42,43].Striking evidence indicates that elevated TSH levels in SH patients do not reflect pituitary

compensation to maintain euthyroidism but mild tissue hypothyroidism *sensu strictu.* Subclinical hypothyroidism alters lipid metabolism, atherosclerosis, cardiac contractility, and systemic vascular resistance.

A large study of women in Rotterdam showed that atherosclerosis and myocardial infarction increased with odds ratios of 1.7 and 2.3 in subclinical hypothyroid women, respectively. Restoration of serum TSH to normal after thyroid hormone replacement improved lipid levels, lowered systemic vascular resistance, and improved cardiac contractility.[44] Patients with subclinical hypothyroidism have prolonged isovolumic relaxation times, whereas systolic contractile function does not change.

Subclinical hypothyroidism is associated with an atherogenic lipid profile, characterized by increased circulating levels of total and low-density cholesterol and increased levels of oxidized low-density lipoproteins (45,46). Flow-mediated vasodilatation, a marker of endothelial function, is significantly impaired in subclinical hypothyroidism (47)

In general, resting heart rate and blood pressure are normal in subclinical hypothyroidism subjects (48-51). An increased prevalence of systemic hypertension have been reported in patients with subclinical hypothyroidism (52,53). The most-consistent cardiac abnormality recognized in SH patients is LV diastolic

dysfunction, characterized by slowed myocardial relaxation and impaired early ventricular filling, both at rest and with exercise [48-51]. In terms of systolic function, [48] documented improvement from pretreatment values, although no difference when compared with the control group. Among measures, parameters of LV morphology were shown to be significantly higher in patients with subclinical hypothyroidism compared with controls [52]. In contrast, Biondi et al. [48] reported no abnormalities of LV morphology seen in the patient group.

TREATMENT

Levothyroxine sodium is the treatment of choice for the routine management of hypothyroidism. Adults with hypothyroidism require approximately 1.7 microg/kg of body weight per day for full replacement. Children may require higher doses (up to 4 microg/kg of body weight per day). Older patients may need less than 1 microg/kg per day. Therapy is usually initiated in patients under the age of 50 years with full replacement. For those patients who are older than 50 years, or in younger patients with a history of cardiac disease, a lower initial dosage is indicated, starting with 0.025 to 0.05 mg of levothyroxine daily, with clinical and biochemical reevaluations at 6- to 8-week intervals until the serum TSH concentration is normalized. Certain drugs, eg, cholestyramine, ferrous sulfate, sucralfate, and aluminum hydroxide antacids, may interfere with levothyroxine

absorption from the gut. The response to treatment of hypothyroidism is predictable, especially from a cardiovascular perspective [53]

Subclinical Hypothyroidism

The treatment of subclinical hypothyroidism remains controversial. It is accepted by some that treatment is indicated in patients with TSH levels >10 μIU/mL or in patients with TSH levels between 5 and 10 μIU/mL in conjunction with goiter or positive anti-thyroid peroxidase antibodies (or both). These patients have the highest rates of progression to overt hypothyroidism. An initial dosage of levothyroxine of 25 to 50μg/day can be used, the serum TSH level should be measured in 6 to 8 weeks, and the levothyroxine dose should be adjusted as necessary. The target TSH level should be between 0.3 and 3.0 μIU/mL. It may improve memory related abilities, depressive features; lipid abnormalities like hypercholesterolemia may also improve. Currently the treatment is recommended only if associated with goiter, anti thyroid antibodies, dyslipidemia, infertilities, menstrual irregularities.

MATERIALS AND METHODS

MATERIALS AND METHODS

The study was conducted in the Out Patient Department, Department of Endocrinology, Institute of Internal Medicine, Madras Medical College & Rajiv Gandhi Government General Hospital, Chennai.

Ethical committee Approval- Obtained

Design of study- Descriptive Study

Sample size - In the study period patients attending the Endocrinology OPD, Institute of Internal Medicine after applying inclusion and exclusion criteria, 80 patients were included in the study. Patients thus selected were divided into three categories according to the level of thyroid stimulating hormone (TSH) as follows:

(i) Mild hypothyroidism (< 20 mIU/ml)

(ii) Moderate hypothyroidism (20 – 50 mIU/ml)

(iii) Severe hypothyroidism (> 50 mIU/ml)

SUBJECTS

Inclusion criterita

1. Female patients older than 18yrs of age
2. Patients with subclinical hypothyroidism (defined as TSH > 5.5μIU/ml with normal free T4 and free T3)
3. Patients with overt hypothyroidism

Exclusion criteria

1. Patients already on treatment with Thyroxine.
2. Patients less than 18 years of age
3. Patients with known primary cardiac disease, DM,Hypertension.
4. Patients who were taking drugs that alter the cardiovascular functions like amiadarone, Beta blockers and calcium channels blockers etc.

Patients attending the Endocrinology outpatient who satisfied the inclusion criteria were registered for the study after obtaining their consent. A detail questionnaire was used to elicit symptoms of hypothyroidism. The patient was examined to look for signs of hypothyroidism. Special attention was given to examination of the cardiovascular system.

All the patients were evaluated for following parameters:

a. Pulse rate
b. Blood pressure - measured thrice and the average was taken (As per recommendations of Joint National Committee – 7)
c. Body mass index (< 25 is normal)
d. Serum total T4 (Normal Range – 5.4–11.7 ug/dL)(54)

e. Serum TSH. (Normal Range – 0.34–4.25 mIU/L)(54) Measurement of total T3 and T4 were done by radioimmunoassay (RIA) technique and TSH levels were measured by Immuno-radiometric assay (IRMA).
f. Chest x ray-For cardiomegaly
g. ECG
h. Total cholesterol (As per recommendations of American National Cholesterol Eradication Programe III)
i. USG neck
j. FNAC thyroid

Echocardiography was done in all the patients and the following parameters were looked for

1. *Chamber dimensions*:

In M Mode transthoracic echocardiogram the LV internal diameter (diastolic), posterior wall thickness and the interventricular septal wall thickness were measured. Reference values for LV linear dimensions as per the **ASE COMMITTEE RECOMMENDATIONS ,2005(54).** Asymmetric hypertrophy is defined as a ratio of interventricular septal thickness and left ventricular posterior wall thickness greater than 1.3.

	Women				Men			
	Reference range	**Mildly abnormal**	**Moderately abnormal**	**Severely abnormal**	**Reference Range**	**Mildly abnormal**	**Moderately abnormal**	**Severely abnormal**
Septal thickness, cm	0.6-0.9	1.0-1.2	1.3-1.5	>1.6	0.6-1	1.1-1.3	1.4-1.6	>1.7
Posterior wall thickness, cm	0.6-0.9	1.0-1.2	1.3-1.5	>1.6	0.6-1	1.1-1.3	1.4-1.6	>1.7
LV diastolic diameter	3.9–5.3	5.4–5.7	5.8–6.1	≥6.2	4.2–5.9	6.0–6.3	6.4–6.8	≥6.9

2. *Diastolic function*:

The E/A ratio is the ratio between early (E) and late (*atrial* - A) ventricular filling velocity (mitral inflow velocity).The early (*E*) diastolic one is caused by accumulation of blood in the atria during previous systole, and second, a late one created by atrial contraction (*A*).

Grading of ventricular diastolic dysfunction

Grade I - abnormal relaxation pattern or diastolic dysfunction with reversal of the normal E/A ratio. This pattern may develop normally with age in some patients and many grade I patients will not have any clinical signs or symptoms of heart failure.

Grade II-Pseudo normal filling dynamics. This is considered moderate diastolic dysfunction and is associated with elevated left atrial filling pressures. These patients more commonly have symptoms of heart failure and many have left atrial enlargement due to the elevated pressures in the left heart.

Grade III-Reversible restrictive diastolic dysfunction. There is reversal of their diastolic abnormalities on echocardiogram when they perform the Valsalva maneuver

Grade IV – Fixed restrictive diastolic dysfunction. No reversibility of their echocardiogram abnormalities.

Grade III and IV are both severe forms of diastolic dysfunction and patients tend to have advanced heart failure symptoms.

3. *Systolic function*:

Echocardiography can measure several parameters as an expression of systolic function of the heart. These parameters are LVEF, fractional shortening, stroke volume and cardiac index, systolic tissue velocity of the mitral annulus and myocardium, strain, and regional wall motion analysis. The Parameters denoting Systolic function [55]) are

Linear method	Women				Men				
	Reference range	Mildly abnormal	Moderately abnormal	Severely abnormal	Reference Range	Mildly abnormal	Moderately abnormal	Severely abnormal	Reference range
Endocardial fractional shortening, %	27–45	22–26	17–21	≤16	25–43	20–24	15–19	≤14	Endocardial fractional shortening, %
Midwall fractional shortening, %	15–23	13–14	11–12	≤10	14–22	12–13	10–11	≤10	Midwall fractional shortening, %
2D Method Ejection fraction, %	**≥55**	**45–54**	**30–44**	**<30**	**≥55**	**45–54**	**30–44**	**<30**	**2D Method** Ejection fraction, %

LV Ejection Fraction = EDV-ESV

---------- X 100

EDV

Grading of systolic dysfunction:

i) Mild - EF 45 to 55 %

ii) Moderate - EF 35 to 45%

iii) Severe - EF < 35%

Fractional Shortening = LVID (D) – LVID(S)

---------- X 100

LVID (D)

This systolic function parameter is now rarely used for diagnosis or clinical decision making

4. *Wall Motion abnormalities*:

For purposes of regional wall motion analysis, the ASE has recommended a 16-segment model or, optionally, a 17-segment model with an addition of the apical cap. The following numerical score is assigned to each wall segment on the basis of its contractile function as assessed visually: 1 = normal (>40% thickening with systole); 2 = hypokinesis (10% to 40% thickening); 3 = severe hypokinesis to akinesis (<10% thickening); 4 = dyskinesis; and 5 = aneurysm. On the basis of this wall motion analysis scheme, a wall motion score index (WMSI) is calculated to semiquantitate the extent of regional wall motion abnormalities

5. *Pericardial Effusion*:

The pericardial effusion is quantified by the amount of echo free space surrounding the heart. The pericardial effusion can be graded as: Minimal pericardial effusion:

Posterior atrio-ventricular groove shows echo free space, this is seen in systolic phase only. It represents normal pericardial fluid.

Mild pericardial effusion: Echo free space < 1cm.

Moderate pericardial effusion: Echo free space 1 – 2 cm.

Large pericardial effusion: Echo free space > 2cm

Statistical analysis

SPSS12 and Excel were used for data analysis.

Consent

All participants gave written informed consent.

Ethical Committee Approval

Institutional Ethical Committee approved the study

RESULTS AND OBSERVATIONS

TABLE: 1 AGE DISTRIBUTION

Age in years	Total (n=80)	Percentage %
21 to 30	30	37
31 to 40	32	40
41to 50	10	13
51 to 60	8	10

80 patients were included in our study of which 30(37%) were in the age group of 21 to 30. Majority , 32(40%) of patients were in the age group of 31 to 40 years of age.10 (13%)patients were in the age group of 41 to 50.About 8(10%) patients were in the age of 51 to 60.The mean age was 35.21 +/- 9.74 Yrs (Range - 21 to 59 Yrs) with SEM (Standard error of mean 1.093)

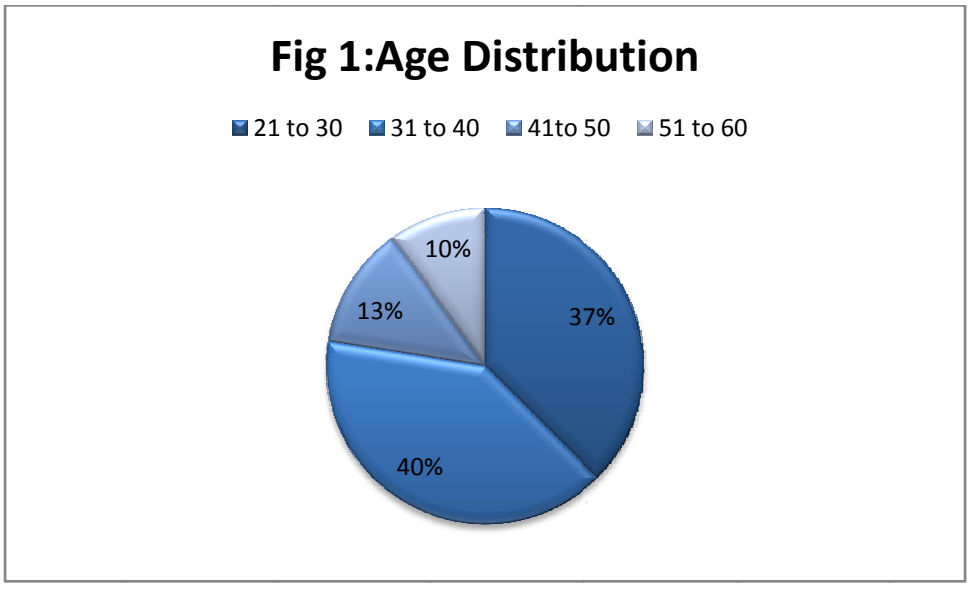


TABLE: 2 SEVERITY OF HYPOTHYROIDISM ACCORDING TO TSH LEVELS

TSH mIU/l	No of patients	Percentage %	Mean	SD
Subclinical	30	38	18.75	8.36
Mild (0.5-20)	12	15	11.32	3.00
Moderate (20-50)	13	16	33.43	10.31
Severe(>50)	25	31	107.58	40.89

Among the 80 patients included in our study, subclinical hypothyroid patients were majority with 30 (38%) in number. Among the hypothyroid patients, 12 (15%) patients had mild hypothyroidism while 13(16%) had moderate hypothyroidism. Severe hypothyroid constituted the rest with 25 in number (31%).The mean TSH in the mild hypothyroid group was 11.32mIU/L ,while among the moderate hypothyroid group was 33.43 mIU/L. The severe hypothyroid group had a mean TSH of 107.58 mIU /L.

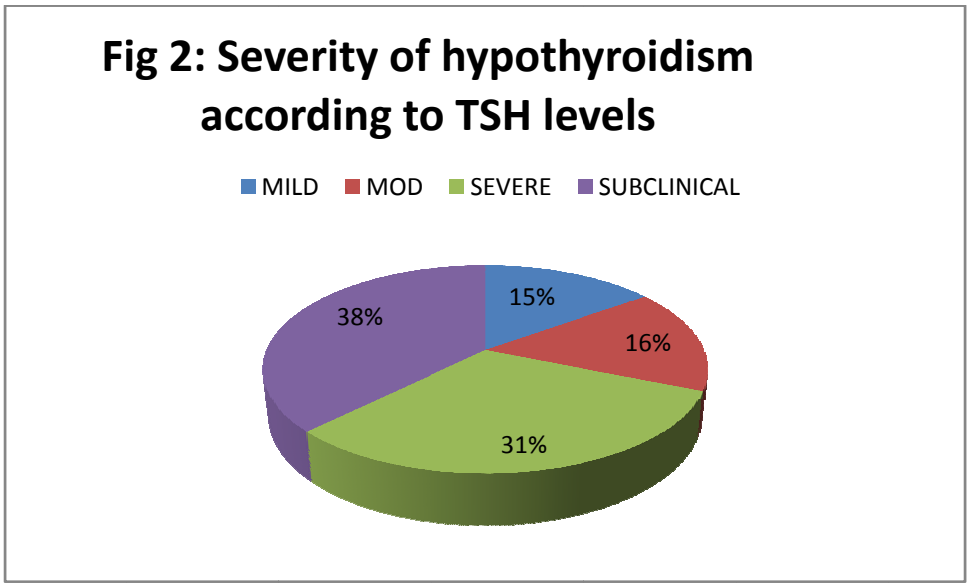


TABLE: 3 METABOLIC PARAMETERS IN HYPOTHYROIDISM

3A. BMI (BODY MASS INDEX)

BMI	Subclinical Hypothyroidism (n=30)	Hypothyroidism (p=0.0019)			Total (n=80)
		Mild (n=12)	Moderate (n=13)	Severe (n=25)	
Normal <25	12	6	6	1	25 (31.25%)
Overweight 25 to 30	10	4	4	10	28 (35%)
Obese >30	8	2	3	14	27 (33.75%)
Mean	27.06	25.75	26.23	30.16	P value = 0.0001
SD	2.9	3.64	3.78	2.95	

The mean BMI in the patients with subclinical hypothyroid was 27.06, while among the mildly hypothyroid it was 25.75. the moderately hypothyroid patients had a mean BMI of 26.23 and the severely hypothyroid was 30.16.The two-tailed P value by the one sample t test is 0.0001, considered extremely significant.

3B. WAIST CICUMFERENCE

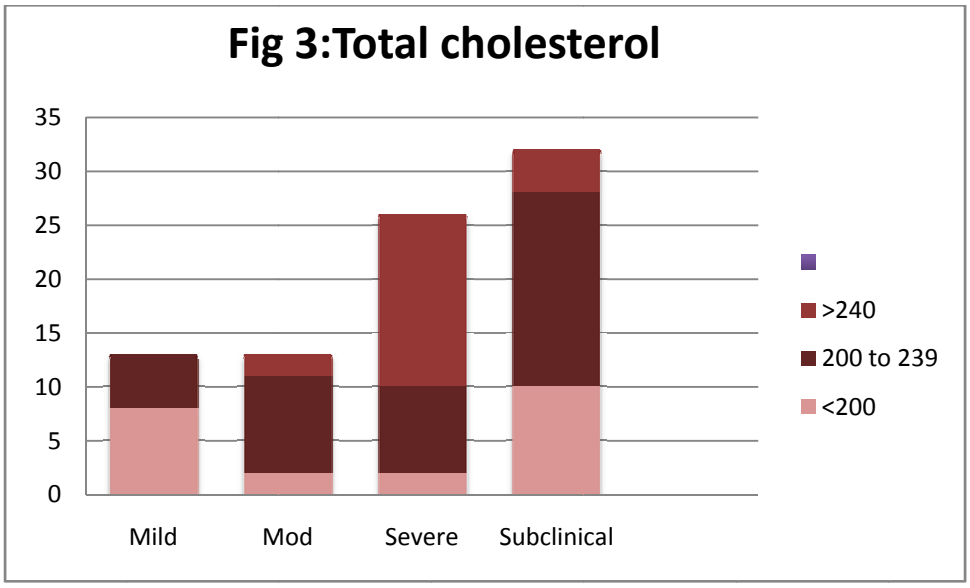
Waist (cm)	Subclinical Hypothyroidism	Hypothyroidism		
		Mild	Moderate	Severe
Female	P= 0.0972			
<88	19(63.33%)	8(66.67%)	7(53.84%)	8(32%)
>88	11(36.67%)	4(33.33%)	6(46.15%)	17(68%)
Mean	83.06	84.91	87.46	89.48
SD	13.44	5.91	6.47	6.00

Among the study population 11 females (36.66%) of the subclinical hypothyroid patients were found to have increased waistline, while 4 females (33.33%) of the mild hypothyroid group had increased waistline. 6 females (46.15%) of the moderately hypothyroid patients and 17 females (68%) were found to have increased waistline. Comparing the means by the One-way Analysis of Variance (ANOVA) p value was 0.0858 not statistically significant.

3C .TOTAL CHOLESTEROL

Total Cholesterol (mg/dl)	Subclinical Hypothyroidism	Hypothyroidism		
		Mild	Moderate	Severe
Normal - <200	10	8	2	2
Borderline - 200 to 239	18	5	9	8
Elevated- >240	4	0	2	16
Mean	217.6	203.16	220.76	253.32
SD	29.93	15.52	30.42	39.63

The Mean Total Cholesterol for mild hypothyroid patients is 203.16 mg /dl while the mean for moderate hypothyroid patients is 220.76 mg/dl. The severely hypothyroid had a mean of 253.32 while the subclinical hypothyroid patients had a mean of 217.6mg/dl.The two-tailed P value by one sample t test is 0.0002 which is statistically significant.



3D.TRIGLYCERIDES

Triglycerides (mg/dl)	Subclinical Hypothyroidism	Hypothyroidism		
		Mild	Moderate	Severe
<150	12	8	9	7
150 TO 199	18	4	4	17
200 TO 499	0	0	0	1
>500	0	0	0	0
Mean	154	134.66	133	165.32
SD	36.56	24.93	33.75	27.69

The Mean Triglycerides for mild hypothyroid patients is 134.66 mg /dl while the mean for moderate hypothyroid patients is 133 mg/dl. The severely hypothyroid had a mean of 165.32 while the subclinical hypothyroid patients had a mean of 154 mg/dl. The P value by Chi-squared Test for Independence is 0.0447 which is statistically significant.

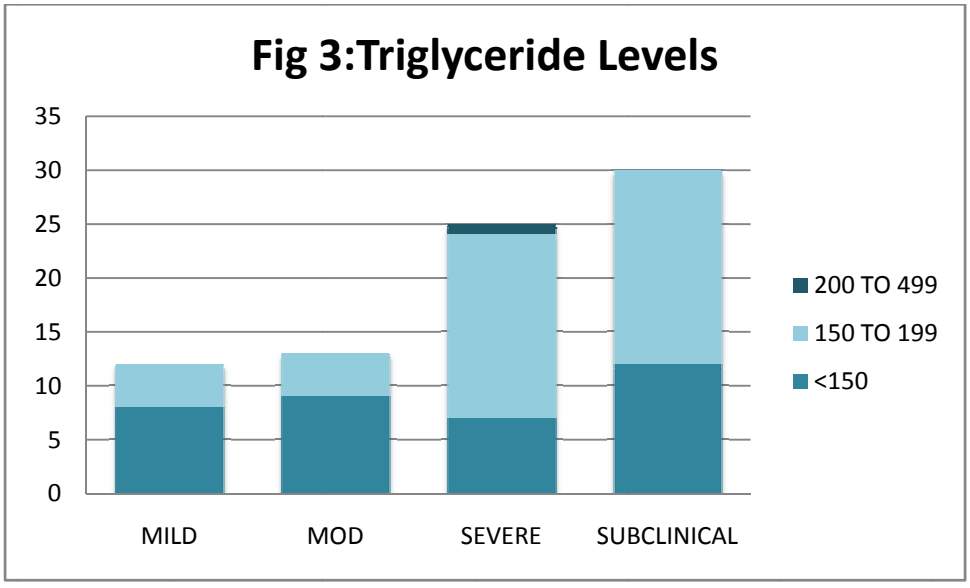
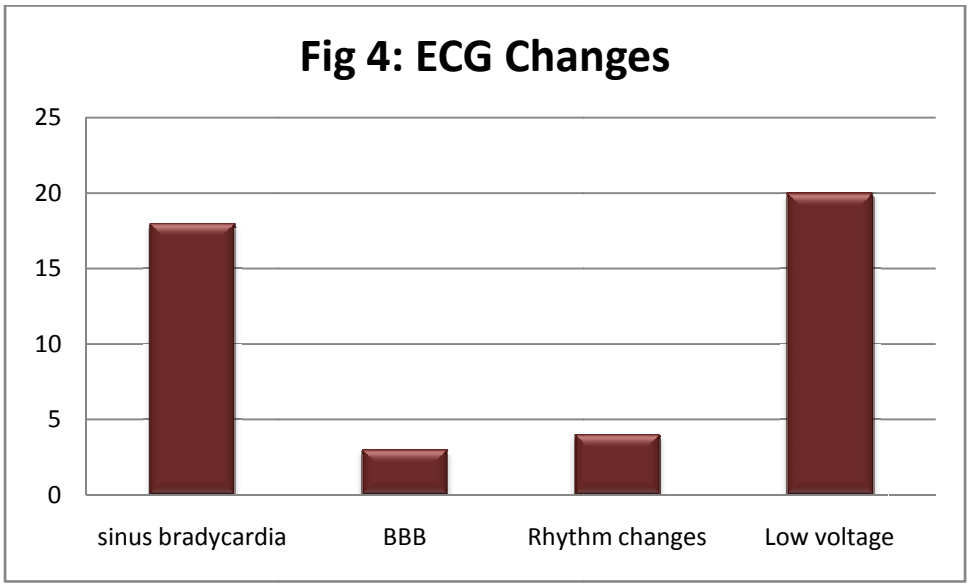


TABLE 4: ECG CHANGES

Abnormalities	Total (n=80)
Sinus Bradycardia	18(22.5%)
BBB	3(3.75%)
Rhythm changes	4(5%)
Low voltage	20(25%)



Low voltage complexes was the commonest ECG finding with 25 %(20) prevalence. Next was Sinus bradycardia found in 22.5% (18). Bundle branch blocks and rhythm changes in the form of atrial fibrillation was found in 3.75% (3) and 5 %(4) respectively.

TABLE:5 MYOCARDIAL WALL THICKNESSES (MM) IN HYPOTHYROID PATIENTS.

5A. LVPW THICKNESS

Types		Reference range (6-9 mm)	Abnormal (>9 mm)	P value
Hypothyroidism	Mild	11	1	0.001327
	Moderate	7	6	
	Severe	7	18	
Total		25	25	
Subclinical Hypothyroidism		28	2	< 0.0001

Among the mildly hypothyroid patients abnormal LVPW thickness was found in 1 (8.3%) and in the moderately hypothyroid it was noted in 6 (46.15%).18 (72%) out of the severely hypothyroid patients had increased LVPW thickness, while this finding was noted in only 2(6.66%) of the subclinical hypothyroid patients. On comparing the occurrence of increased LVPW thickness with increasing severity of disease by the Chi-squared Test for Independence the P value is 0.0013 and on comparing the hypothyroid with the subclinical hypothyroid patients by the Fisher's Exact Test the two-sided P value is < 0.0001 with Relative risk = 7.132.

5B.IVS THICKNESS

Types		Reference range (6-9 mm)	Abnormal (>9 mm)	P value
Hypothyroidism	Mild	11	1	0.0007
	Moderate	4	9	
	Severe	7	18	
Total		22	28	
Subclinical Hypothyroidism		25	5	0.0009

Among the mildly hypothyroid patients abnormal septal wall thickness was found in 1 (8.3%) and in the moderately hypothyroid it was noted in 9 (69.23%).18 (72%) out of the severely hypothyroid patients had increased septal wall thickness, while this finding was noted in only 5(16.66%) of the subclinical hypothyroid patients. On comparing the occurrence of increased septal wall thickness with increasing severity of disease by the Chi-squared Test for Independence the P value is 0.0007and on comparing the hypothyroid with the subclinical hypothyroid patients by the Fisher's Exact Test the two-sided P value is 0.0009 with Relative risk = 0.5280.

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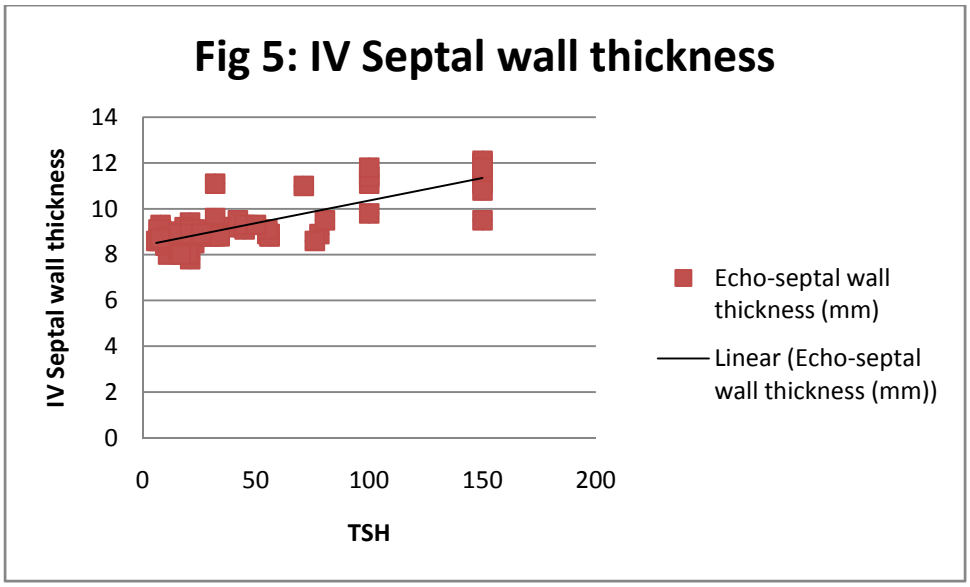
Fig 5: IV Septal wall thickness
IV Septal wall thickness
14
12
10
8
6
4
2
0
0
50
100
150
200
TSH
Echo-septal wall thickness (mm)
Linear (Echo-septal wall thickness (mm))

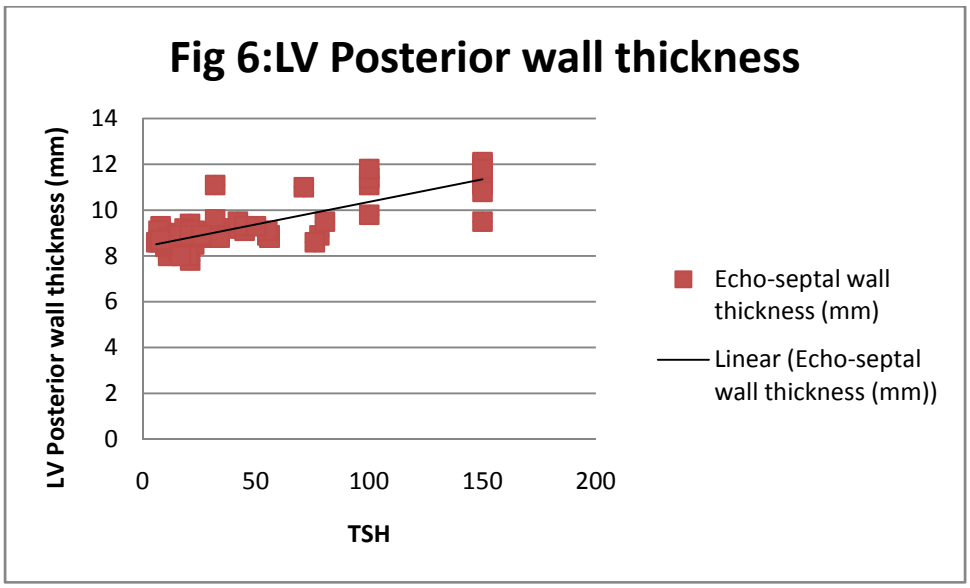
Fig 6:LV Posterior wall thickness
LV Posterior wall thickness (mm)
14
12
10
8
6
4
2
0
0
50
100
150
200
TSH
Echo-septal wall thickness (mm)
Linear (Echo-septal wall thickness (mm))

TABLE: 6 CARDIAC CHAMBER SIZE (CM) IN HYPOTHYROID PATIENTS

LVID(D) cm (p=0.6250)	**Subclinical Hypothyroidism**	**Hypothyroidism**		
		Mild	**Moderate**	**Severe**
<5.4	12	13	24	30
>5.3	0	0	1	0

The Cardiac chamber size was found to be normal in the study population .On statistical analysis with Fisher exact probabilities test the p value was 0.6250, statistically insignificant showing that the cardiac chamber size is not affected by hypothyroidism .

TABLE :7 LV SYSTOLIC FUNCTIONS IN HYPOTHYROID PATIENTS

Parameters	Types	EF (%)		FS (%)		RWMA	Global Hypokinesia
		>55%	<55%	>30%	<30%		
Subclinical Hypothyroidism		30	0	30	0	0	0
Hypothyroidism	**Mild**	12	0	12	0	0	0
	Moderate	12	1	13	0	0	0
	Severe	23	2	25	0	0	0
P value		0.2911		1		-	-

On statistical analysis of the ejection fraction and fractional shortening with the severity of the disease, the p values were >0.05 and not significantly associated. Thus the LV systolic functions as measured by ejection fraction and fractional shortening were not associated with the severity of hypothyroidism. No wall motion abnormalities or global hypokinesia was detected. Only 2 (8%) of the severely hypothyroid group and 1(7.69%) in the moderately hypothyroid group had reduction of ejection fraction.

TABLE 8: DIASTOLIC DYSFUNCTION IN HYPOTHYROIDISM

Types		**E/A Ratio**		**P value**
		>1	**<1**	
Hypothyroidism	Mild	11	1	0.1714
	Moderate	11	2	
	Severe	16	9	
Total		38	12	
Subclinical Hypothyroidism		27	3	0.1481

Diastolic dysfunction was found in 1(8.33%) patient in the mild hypothyroid group and in 2 (15.38%) of the moderately hypothyroid group.9 (36%) patients of the severely hypothyroid group had diastolic dysfunction. In the subclinical hypothyroid group the same was noted in 3(10%) patients.

TABLE: 9 ANALYSES OF THE MEANS OF ECHO PARAMETERS

Mean values	Subclinical Hypothyroidism	Hypothyroidism			P value
		Mild	Moderate	Severe	
LVPW(mm)	8.49	8.74	9.23	10.54	< 0.0001
IVSW(mm)	8.74	8.75	9.20	10.42	< 0.0001
LVID(D)cm	4.44	4.51	4.41	4.58	0.4542
EF %	62	63.08	61.61	61.6	0.8967
FS %	33.86	34.08	34.16	34.44	0.8260
E/A	1.50	1.69	1.62	1.25	0.0098

On statistical analysis by one way analysis of variance (ANOVA) it was found that LVPW (mm) ,IVSW(mm) and E/A were significantly associated with the severity of hypothyroidism, while EF %, FS %and LVID (D)cm were significantly not associated.

TABLE 10: PERICARDIAL INVOLVEMENT IN HYPOTHYROID PATIENTS

Pathology	Subclinical Hypothyroidism	Hypothyroidism		
		Mild	Moderate	Severe
Mild PE	1	1	2	2
Mod PE	0	0	1	6
Large PE	0	0	1	2
Pericardial thickening	0	0	0	0
Constrictive physiology	0	0	0	0
Total	1	1	4	10

Pericardial effusion was observed in 1(8.33%) of the mild hypothyroid patients, and also in 4 (30.76%) patients of the moderately hypothyroid group. 10 (40%) of the severely hypothyroid had the same .No pericardial thickening or Constrictive physiology was made out.

TABLE 11: AGE AND CHAMBER THICKNESS

Age	MEAN LVPW (MM)	MEAN IVSW (MM)
20-29	9.21+/- 1.1	9.15+/-0.88
30-39	9.56+/-1.29	9.69+/-1.2
40-49	8.4 +/- 0.63	8.4+/- 0.63
50-59	9.81+/-1.59	9.54+/- 1.3
P VALUE	< 0.0001	< 0.0001

There was a trend of increasing wall thickness with age in the patients.

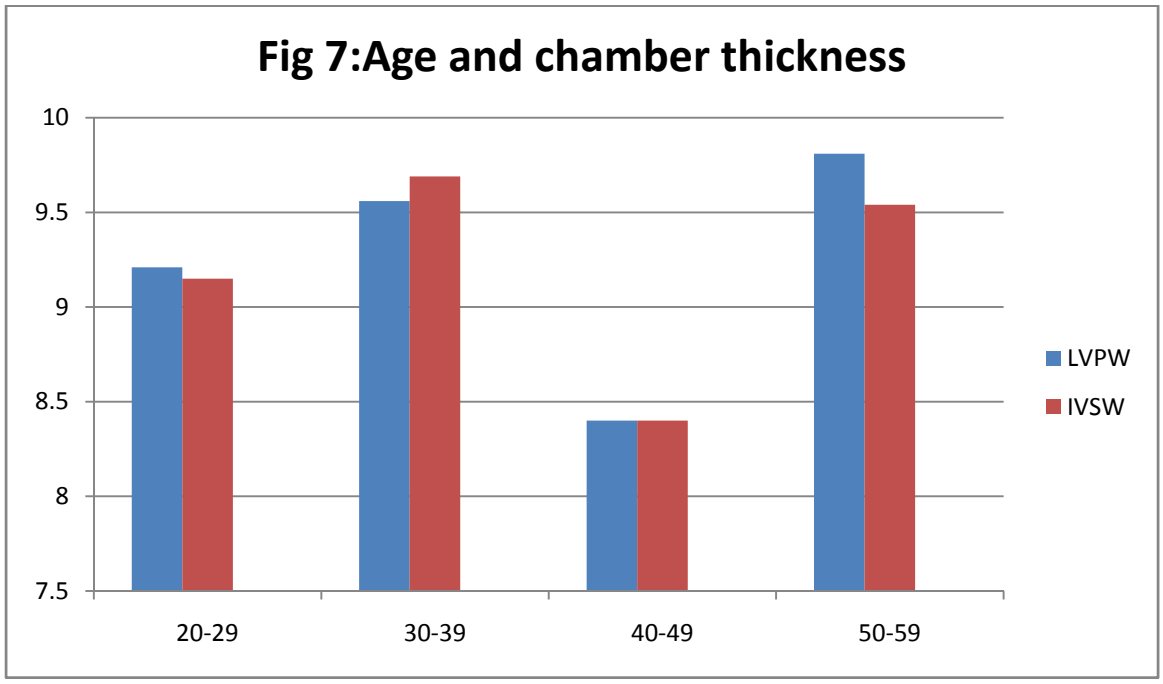

TABLE 12: MULTIPLE REGRESSION ANALYSIS WITH DEPENDENT VARIABLE IV SEPTAL WALL THICKNESS AND INCLUDING AGE AND SEVERITY OF HYPOTHYROIDISM

VARIABLE	COEFFICIENT	SE	95% CONFIDENCE INTERVAL	T RATIO	P VALUE
CONSTANT	3.695	0.7572	2.170 TO 5.221	19.220	< 0.0001
AGE	-0.002064	0.008946	-0.02009 TO 0.01596	0.5324	0.8186
TSH	0.008883	0.002195	0.004461 TO 0.01331	9.970	0.0002

R squared 0.8387

Adjusted R squared 0.8281

A multiple regression analysis was done with the dependent variable as IV septal wall thickness and entering the significant items, including age and TSH as variable, it was found that only TSH continued to be significant.

TABLE 13: MULTIPLE REGRESSION ANALYSIS WITH DEPENDENT VARIABLE LVPW THICKNESS AND INCLUDING AGE AND SEVERITY OF HYPOTHYROIDISM

VARIABLE	COEFFICIENT	SE	95% CONFIDENCE INTERVAL	T RATIO	P VALUE
CONSTANT	7.995	0.5247	6.938 TO 9.051	15.236	< 0.0001
AGE	0.01518	0.01494	- 0.01491 TO 0.04527	1.016	0.3149
TSH	0.01919	0.002430	0.01430 TO 0.02408	7.898	< 0.0001

R squared 0.5930

Adjusted R squared 0.5756

A multiple regression analysis was done with the dependent variable as LVPW thickness and entering the significant items, including age and TSH as variable, it was found that only TSH continued to be significant.

DISCUSSION

DISCUSSION

The cardiac complications of long standing hypothyroidism are serious if are not diagnosed properly earlier. Echocardiography as a non-invasive method can play important role in recognizing the cardiac pathology as well as to follow up effect of the therapy.

In this study of Indian population, we evaluated the cardiovascular function in newly detected primary overt and subclinical hypothyroidism. 80 patients were included in our study of which 37% were in the age group of 21 to 30. Majority of the patients were in the age group of 31 to 40 years of age with 40% prevalence. 13% patients were in the age group of 41 to 50.About 10% patients were in the age of 51 to 60.The mean age was 35.21 +/- 9.74 Yrs.

Among the 80 patients included in our study, subclinical hypothyroid patients were majority with 38% in number. Among the hypothyroid patients, 15% patients had mild hypothyroidism while 16% had moderate hypothyroidism. Severe hypothyroid constituted the rest with 31%.

Metabolic parameters in Hypothyroidism

In our study we found that the mean BMI in the patients with subclinical hypothyroid was 27.06, while among the mildly hypothyroid it was 25.75. The moderately hypothyroid patients had a mean BMI of 26.23 and the severely

hypothyroid was 30.16. BMI was significantly associated with the severity of the disease. Among our study population 36.66% of the subclinical hypothyroid patients were found to have increased waistline, while 33.33% of the mild hypothyroid group had increased waistline. 46.15% of the moderately hypothyroid patients and 68% were found to have increased waistline.

This is similar to the observations by Brunilda Figueroa et al [56] who in their study found that the mean TSH level was 2.2 mU/L for women and 1.9 mU/L for men. Mean BMI was 32.8 kg/m 2 for women and 35.9 kg/m for men. Females had a mean fat percent of 38.1% and males had 31.4% in their study.

However Manji et al [57] found no association between serum TSH and free T3 concentrations within the normal range and BMI. In contrast, Knudsen et al [58] found that thyroid function could be one of several factors that act in concert to determine body weight.

Dyslipidemia is a common finding in patients with not only overt but subclinical hypothyroidism also, mainly concerning total and LDL cholesterol and less often HDL cholesterol, triglycerides, lipoprotein (a), apolipoprotein A1, and apolipoprotein B. Dyslipidemia coexists with various metabolic abnormalities and induce insulin resistance and oxidative stress via a vice-vicious cycle. The above associations in combination with the thyroid hormone induced hemodynamic

alterations, might explain the increased risk of coronary artery disease, cerebral ischemia risk, and angina pectoris in older patients.

In our study the Mean Total Cholesterol for mild hypothyroid patients is 203.16 mg /dl while the mean for moderate hypothyroid patients is 220.76 mg/dl. The severely hypothyroid had a mean of 253.32 while the subclinical hypothyroid patients had a mean of 217.6mg/dl. The Mean Triglycerides for mild hypothyroid patients is 134.66 mg /dl while the mean for moderate hypothyroid patients is 133 mg/dl. The severely hypothyroid had a mean of 165.32 while the subclinical hypothyroid patients had a mean of 154 mg/dl. Both these lipid parameters were found to be statistically significantly associated with the severity of hypothyroidism.

Similar findings, that hypothyroidism is associated with an atherogenic lipid profile was shown by O'Brien T et al [(59)] in a study of 268 patients with primary hypothyroidism and 27 with secondary hypothyroidism, who were examined in the Thyroid Clinic at the Mayo Clinic during a 1-year period. They were reviewed found significant associations of total thyroxine with total cholesterol and triglycerides and thyroid-stimulating hormone with total cholesterol and low-density lipoprotein cholesterol.

ECG Changes

In our study low voltage complex was the commonest ECG finding with 25 % prevalence. Sinus bradycardia was found in 22.5%. Bundle branch blocks and rhythm changes in the form of atrial fibrillation was found in 3.75% and 5 % respectively. This was in accordance with the known ECG changes which are expected to occur in hypothyroidism. Prolongation of the QT interval, decreased P-wave voltage, prolonged AV conduction time, intraventricular conduction disturbances, and nonspecific ST-T-wave abnormalities were not observed in our study population.

Myocardial wall thickness in hypothyroidism

Alvani D. Santos et al [(60)] first reported in 1979 a reversible cardiomyopathy, manifested by asymmetric septal hypertrophy in untreated hypothyroid patients. Among the mildly hypothyroid patients abnormal LVPW thickness was found in 1 patient and in the moderately hypothyroid it was noted in 6 patients .18 out of the severely hypothyroid patients had increased LVPW thickness, while this finding was noted in only 2 of the subclinical hypothyroid patients. Significant association was found between the occurrence of increased LVPW thickness and the severity of disease.

1 among the mildly hypothyroid patients had abnormal septal wall thickness and in the moderately hypothyroid it was noted in 9 patients.18 of the severely hypothyroid patients had increased septal wall thickness, while this finding was noted in only 5 of the subclinical hypothyroid patients. On comparing the occurrence of increased septal wall thickness with increasing severity of disease it was found to be statistically significant.

Rawat and Satyal [61]) in their study showed relatively increased thickness of IVS and LVPW (1.2/1.7 and 1.1/1.6 cm) when compared to the treated patients (0.9/1.4 and 0.9/1.3 cm) or control subjects (0.8/1.3 and 0.7/1.2 cm). But on age group analysis it was found that this difference was more marked in older patients. In our study however we found that although there was a trend of increasing wall thickness with age these changes on multiple regression analysis with the dependent variable as IVseptal wall thickness and LVPW thickness including age and TSH as variable, it was found that only TSH continued to be significant.

Jagdish et al [62] in their study showed that IVS and LVPW thickness decreased after treatment from 11.77 ± 1.73 to 11.33 ± 109 and 11.97 ± 1.83 to 11.40 ± 1.06 respectively .

Cardiac chamber size in hypothyroidism

The Cardiac chamber size was found to have a statistically insignificant association with hypothyroidism. This shows that the cardiac chamber size is not affected by hypothyroidism. Similar observations were also made by Varma R et al (63).

LV functions

The LV systolic functions as measured by ejection fraction and fractional shortening were not statistically associated with the severity of hypothyroidism. No wall motion abnormalities or global hypokinesia was detected. Only 2 (8%) of the severely hypothyroid group and 1(7.69%) in the moderately hypothyroid group had reduction of ejection fraction

In the study by Jagdish et al (62), although FS increased from 26.43 ± 2.79 to 26.73 ± 2.64 and EF showed increased from 53.93 ± 5.50 to 54.83 ± 4.64 , it was statistically not significant. Rawat et al (61) showed no significant change in parameters of systolic function while Monzani et al (64) found that FS and thus systolic function of LV significantly improved after treatment.

In our study diastolic dysfunction was found in 1(8.33%) patient in the mild hypothyroid group and in 2 (15.38%) of the moderately hypothyroid group.9 (36%) patients of the severely hypothyroid group had diastolic

dysfunction.. Similar findings of diastolic dysfunction were made by Almira Hadžovic-Džuvo et al [65], and Rajan et al [66]. Biondi B,et al [67] in their study of subclinical hypothyroid patients showed significant prolongation of the isovolumic relaxation time (94 +/- 13 vs. 84 +/- 8 msec; P < 0.001), increased A wave (55 +/- 13 vs. 48 +/- 9 cm/sec; P < 0.05), and reduced early diastolic mitral flow velocity/late diastolic mitral flow velocity ratio (1.4 +/- 0.3 vs. 1.7 +/- 0.3; P < 0.001) indicating an early diastolic dysfunction. In our study diastolic dysfunction was noted in 3(10%) patients of the subclinical hypothyroid group which was insignificant.

Pericardial pathology in Hypothyroidism

Pericardial effusion may occur in 30 % to 80% of patients with hypothyroidism. Pericardial effusion was observed in 1(8.33%) of the mild hypothyroid patients, and also in 4 (30.76%) patients of the moderately hypothyroid group. 10 (40%) of the severely hypothyroid had the same .No pericardial thickening or Constrictive physiology was made out. There was a striking correlation between severity of disease and pericardial effusion.

LIMITATIONS OF STUDY

LIMITATIONS

1. The study was done on a sample of patients in the outpatient department. This makes the results of the study less generalizable to the overall population of hypothyroid patients.
2. The sample size of 80 was relatively small to detect fine associations especially in the presence of multiple confounding variables.
3. The cross sectional nature of the study makes it possible that the conclusions made may be unstable, or that they may be reflective of a phenomenon particular to one phase of illness.
4. The follow-up of the patients after replacement of thyroxine was not done due to several reasons. If done it could have highlighted more on the reversibility of the cardiovascular changes.

CONCLUSION

CONCLUSION

1. Increased interventricular septal and left ventricular posterior wall thicknesses with diastolic dysfunction are some of the earliest cardiac features of progressive thyroid failure.
2. The magnitude of the lipid changes and the subtle impairment of left ventricular diastolic function in subclinical hypothyroidism patients as shown in our study may justify use of hormone replacement even without overt cardiac symptoms.
3. An early diagnostic approach in patients with hypothyroidism will surely diminish the extent of cardiac complication which accompanies it.
4. Echocardiography is a useful noninvasive tool in assessing the response to replacement therapy.

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PROFORMA

Name: Age: Sex:

Address: Presentation: First/ Refferal

Occupation:

Op\IP No: Contact no:

SYMPTOMS: Duration

Asymptomatic Fatigue /Irritability

Neck swelling Depression / Anxiety

Skin changes Weight gain /loss

Cold /Heat intolerance Sleepiness/ Insomnia

Hair loss Myalgia/arthralgia

Muscle cramps /weakness Hard of hearing /Hoarseness of voice

Constipation /Loose stools/other bowel symptoms

Breathlessness /Chestpain/ Palpitation /Syncope

PAST HISTORY:

CAD Dyslipidemia DM

Hypertension TB Thyroidectomy

Any other relevant past history

PERSONAL HISTORY:

Alcohol Drug abuse Smoking

MARITAL STATUS: Married/unmarried

MENSTRUAL HISTORY: Amenorrhea / oligomenorrhea /Menorrhagia /Menopause

OBSTETRIC HISTORY: Secondary /primary Infertility

TREATMENT HISTORY: H/oDrugs (Thyroxin / Lithium /Amiadarone /antithyroid /Interferon), Radio iodine, H/o neck Radiation.

SALT INTAKE: Iodised / non iodised

GENERAL EXAMINATION:

Built Nourishment

Height: Weight: BMI

Pallor Icterus Cyanosis Clubbing

Lymphadenopathy Edema

Pulse rate: BP: RR:

Temp:

Peripheral pulses

Facies -Anxious/dull/ normal

Eyes-Periorbital Puffiness /protruding/normal

Skin -Dry Coarse/wet

Loss of Hair

THYROID:

Diffuse/Nodular/Thyroidectomy scar

CVS

RESPIRATORY SYSTEM

ALIMENTARY SYSTEM

MUSCULO SKELETAL

NERVOUS SYSTEM

INVESTIGATIONS

TFT- T3 T4, fT4 TSH

FLP- T. CHOLESTEROL, LDL, HDL, TG

Hb ESR Blood sugar

ECG

ECHOCARDIOGRAPHY

Septal wall thickness	LV Posterior wall thickness
Fractional shortening	Ejection fraction
Diastolic dysfunction (E/A ratio)	LVID
Pericardial effusion	RWMA
Hypokinesia	